#9 3/8/02 T.Bray

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE		
	Application Number	09/580,281
	Filing Date	26 May 2000
	First Named Inventor	J. Michael McINTOSH
	Group Art Unit	1653
	Examiner Name	G. Bugaisky
	Attorney Docket Number	2314-187
Title of the Invention:	CONOTOXIN PEPTIDES	

RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the Office Action mailed 2 October 2001, the Examiner restricted the claims into four Groups. Applicants provisionally elect Group I. As a species of the peptide, Applicants elect the peptide Mar1 having an amino acid sequence set forth in SEQ ID NO:2. If further required, Applicants elect Xaa_1 as Tyr, Xaa_2 as Lys and Xaa_3 as hydroxy-Pro. Claims 1-5, 13 and 19-26 read on peptide Mar1 and the specified species of Mar1. This election is made with traverse.

There are two criteria for a proper requirement for restriction between patentably distinct inventions: 1) The inventions must be independent or distinct as claimed; and 2) There must be a serious burden on the Examiner if restriction is not required. See MPEP § 803. Examiners must provide reasons and/or examples to support conclusions. For purposes of the initial requirement, a serious burden on the Examiner may be *prima facie* shown if the Examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant. Insofar as the criteria for restriction practice relating to Markush-type claims is concerned, the criteria are set forth in MPEP § 803.02. See MPEP § 803. If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the Examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions. In such a case, the Examiner will not require restriction. See MPEP § 803.02.

Concerning the claims of the present application, claims 1-26 and 29 are drawn to a series of conotoxin peptides (referred to hereinafter as conopeptides). Applicants agree that the various conopeptides are distinct from each other. However, as stated in the MPEP, as discussed above, distinctness alone is not enough to require a restriction. There must also be a serious burden upon the examiner. In the absence of such a burden, the examiner must examine all of the claims (or in this case, it is urged that all of the peptide claims should be examined). It is urged that the burden of examining all of the peptide claims of the present application is not a serious one, and that the burden of examining all of the peptide claims is only slightly greater than examining one of the groups of claims.

The examination entails various aspects. First is a decision concerning utility under 35 U.S.C. §101. Although each peptide species being claimed is distinct, they are all related in their structure and biological activity. Consequently, a decision concerning utility will be identical for all of the species, and there is no added burden of examining all of the species as compared to examining only a single species.

The second aspect of examination is whether the provisions of the various paragraphs of 35 U.S.C. § 112 have been met. In general, and in this case, this means reviewing the application and claims for compliance with paragraphs 1 and 2 of § 112. As for the enablement aspect as found in paragraph 1 of § 112, all of the peptides are related in their structure and biological activity. Since no basis for distinguishing between the enablement of one species vs. another species has been set forth, it is presumed that all of the listed peptides will be treated equally. Again, this means that only a single decision needs to be made concerning all of the peptides. Therefore, this aspect of the examination will not be a serious burden if all peptides are examined, vs. only one of the peptides.

Concerning paragraph 2 of § 112, this involves the wording of the claims. The wording of the claims in each group of claims is identical except for the specified peptide. Consequently, any objections to the language of the claims for one Group of claims is equally applicable to the other Groups of claims. Therefore, there is no increase in the burden concerning 35 U.S.C. § 112, second paragraph, if all peptide claims are examined.

The third aspect of examination is a review of prior art to determine whether the claims are anticipated or obvious. There are two aspects of such a search. A first aspect is a review of the prior art literature and patents. The literature to be reviewed will be identical for all of the peptides. All of the claimed peptides have similar, though not identical, structures and all are claimed to have the same utility. The Examiner has not stated that a search of the scientific literature will be any different for one peptide than for any other peptide. The Office Action states that all of the peptides are classified in class 514, subclass 514. That is, a single subclass covers all of the methods and a single subclass covers all of the peptides. Consequently the search of the patent literature will clearly be the same for all of the peptides. Because the search of the scientific literature and patent literature will be identical for all of the peptides, there is no added burden concerning this aspect if all of the peptides are examined. Furthermore, the search will probably entail a computer search based on the peptide sequences in the sequence listing. It is believed that such a search would identify prior art directed to the claimed peptides or peptides having the specified substitutions.

Consequently, it is submitted that the only reason for restriction is that the peptides are distinct from each other. But as explicitly stated in MPEP § 803, the inventions must be distinct and there must be a serious burden on the examiner. MPEP § 803.02 states that if a search and examination of an entire claim can be made without serious burden, the examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions. As urged above, it is asserted that examination of all of the peptides claims will not impose a serious burden.

Furthermore, Applicants assert that each claimed sequence with its Xaa designators is, in effect, a chemical genus. Each range of amino acids given for a single Xaa designator is a narrow range of chemical side chains well known in the art to result in little to no change in activity upon substitution into peptide chains. Applicants submit that each species represented by the Xaa designators share a common utility (e.g., analgesic activity) and a substantial structural feature disclosed as being essential to that utility (the conserved cysteine spacing, conserved disulfide bridging pattern, and conserved non-cysteine residues as indicated in the generic formula of claim 1). Applicants further submit that each substitution, e.g. hydroxy-Pro versus Pro, results in a species that would be unpatentable, due to obviousness over the other claimed species. Thus, Applicants

believe that restriction between various amino acids represented by the Xaa designators is not proper in this case.

As is well known in the art, a particular class of conotoxins will share a conserved cysteine framework, disulfide bridging pattern, conserved non-cysteine residues, and conserved molecular target. For example, it is known that α-conotoxins all share the following conserved four cysteine spacing (CC----C-----C), with the first and third cysteines forming a disulfide bridge and the second and fourth cysteines forming a disulfide bridge. Additionally, all α-conotoxins contain a conserved proline between the second and third cysteines. These conserved structural elements serve to form a very characteristic three-dimensional structure for the α-conotoxins (see the attached Figure 1). Note that the backbones of each α-conotoxin shown in the attached Figure 1 are superimposeable. Other than the conserved elements mentioned above, the sequences of the α-conotoxins are quite divergent.

Additionally, the gene organization for all conotoxins have been characterized. As shown in the attached Figure 2, each toxin is found at the C-terminal (3') end of the gene. There are two regions upstream of the toxin sequence in the gene. First, is a signal sequence used to target the protein into the appropriate cellular compartment in the venom-producing cells of the cone snails. This is followed by an intervening pro region whose function has not been determined. Analysis of sequences across all known conotoxin families have determined a very unexpected finding. All members of a conotoxin family share a conserved signal sequence that is different from that of even closely related families. For example, there are two families of conotoxins that share the same cysteine framework and disulfide bridging pattern (--C----C---CC---C----C--). They are the ω-conotoxins and the δ-conotoxins. However, the ω-conotoxins all inhibit subtypes of Ca^{+2} channels, while the δ-conotoxins all inhibit Na^{+} channel subtypes. Even though these two families share the same cysteine framework and disulfide bridging pattern, they have evolved to inhibit different molecular targets. It was found that the signal sequence of the ω-conotoxins differs significantly from that of the δ-conotoxins. Thus, the sequence of the signal sequence is predictive of a shared target in the nervous system.

Finally, the biological effects of α-conotoxins appears to be diverse when delivered into model animals. However, it has been well established for EVERY α-conotoxin investigated to date that they all target nicotinic acetylcholine receptors with high affinity and selectivity. Thus, the conserved elements listed previously serve to confer a specific three-dimensional shape and a conserved function (the inhibition of nicotinic acetylcholine receptors). The conserved three-dimensional structure of each conotoxin is equivalent to a conserved chemical core found in the chemical genus often searched and patented by the PTO. The divergent sidechains amount to limited R-groups which are readily searched and allowed by the PTO. To make a distinction between a peptidic chemical genus is arbitrary and absurd.

The divergent biological effects observed for each α-conotoxin are due to differences in function and localization for the various nicotinic acetylcholine receptors targeted by the α-conotoxins. Thus, the α-conotoxins form a group of highly structurally and functionally related compounds. The same is true for other families of conotoxins that have been characterized (δ-conotoxins target Na^+ channels, ω-conotoxins target Ca^{+2} channels, etc.) The Examiner's attention is further directed to McIntosh et al. (*Conus* Peptides as Probes for Ion Channels, Methods in Enzymology, Vol. 294, pp. 605-624, 1999), copy attached hereto, for a review of conotoxin families that goes into detail of the conservation within conotoxin families.

This application describes a novel family of conotoxins which each have a conserved cysteine spacing, a conserved disulfide bridging pattern, and (based upon results with all previous conotoxins) a conserved molecular target. See the following Table.

Table -- Alignment of Conotoxins

U036	-GI**CC**G**C**VSF**C**Y**C**-**C**
Q819	-QT**CC**G**C**YRM**C**V**C**-**C**
Q820	-ST**CC**G**C**FKM**C**I**C**-**C**R
Mar2	-GV**CC**G**C**YKL**C**H**C**-**C**
Mar1	NGV**CC**G**C**YKL**C**H**C**-**C**
Q818	--A**CC**G**C**YKL**C**S**C**-**C**

Thus, it is submitted that each sequence given in the claims represents a species of the conotoxin genus. Since all the species share a common structural motif and a common function, Applicants believe that restriction between the various species of this genus is unwarranted.

In view of the above arguments, it is requested that the restriction requirement imposed in the Office Action mailed 2 October 2001 be reconsidered and that all of claims 1-26 and 29 be examined together.

RESPECTFULLY SUBMITTED,					
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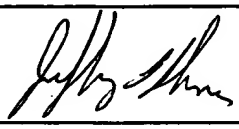
SIGNATURE				DATE	3 December 2001
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